PATENT SPECIFICATION

NO DRAWINGS

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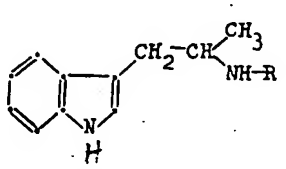
COMPLETE SPECIFICATION

Novel Tryptamine Derivatives and a process for the manufacture thereof

We, ROCHE PRODUCTS LIMITED, a British Company, of Broadwater Road, Welwyn Garden City, Hertfordshire, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with novel tryptamine derivatives and with a process for the manufacture thereof; more particularly, the invention is concerned with certain N - alkyl - α - methyl tryptamines and acid addition salts thereof and with a process for the manufacture of same.

The novel tryptamine derivatives provided by the invention are compounds of the following general formula:



in which R stands for the methyl or ethyl group, and pharmaceutically acceptable acid addition salts thereof. These secondary amines, like the known α-methyl-tryptamine, possess psychostimulant properties. The corresponding compounds having higher N-alkyl groups are either inactive or insignificantly active.

According to the process provided by the invention, the novel substances aforesaid are manufactured by formylating or acetylating 3 - (2' - amino propyl) - indole and reducing the carbonyl group of the resulting formyl or acetyl compound to the methylene group and, if desired, converting the resulting base into a pharmaceutically acceptable acid addition salt thereof.

The first step of the process, namely the acylation of the 3-(2'-amino-propyl)-indole, is preferably carried out using the appropriate aliphatic acid anhydride (the mixed anhydride product of the reaction of acetic acid anhydride and formic acid where it is desired to formylate). The use of a solvent is not necessary for the carrying out of this step.

The reduction of the carbonyl group in the product of the first step to a methylene group is suitably carried out using lithium aluminium hydride. Tetrahydrofuran is a suitable solvent in which to carry out the reduction.

The pharmaceutically acceptable acid addition salts may be prepared by simply reacting the reduction product with the appropriate acid, preferably in a solvent. Examples of acids are hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, tartaric acid and citric acid.

The derivatives of the invention may be used as medicaments in the form of pharmaceutical preparations, which contain the compounds or salts thereof in admixture with an organic or inorganic, solid or liquid pharmaceutical carrier suitable for enteral (e.g. oral) or parenteral administration. For making up the preparations there may be employed substances which do not react with the compounds, such as water, gelatine, lactose, starches, magnesium stearate, talc, vegetable oils, gums, polyalkylene glycols, petroleum jelly or any other known carrier used for the preparation of medicaments. The pharmaceutical preparations may be in solid form, for example, as tablets, dragees, suppositories or cupsules, or in liquid form, for example, as solutions, emulsions or suspensions. If desired, they may be sterilized and/or contain auxiliary substances, such as preserving agents, stabilizing agents, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers. They may also contain, in

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combination, other therapeutically useful substances.

The following examples illustrate the process of the invention:—

EXAMPLE 1

Acetic anhydride (48 mls $\equiv 2 \times 0.255$ mols) and formic acid (19.1 mls $\equiv 2 \times 0.255$ mols) are mixed, with shaking and cooling if necessary, and the mixture is then heated at 60°C for 2 hours, after which time it is cooled to 20°C.

3 - (2^1 - Amino - propyl) - indole (44.4 g $\equiv 0.255$ mols) is now added in small portions, with stirring and cooling, until a clear solution is obtained. The mixture is then allowed to stand at 20°C for 16—18 hours. The bulk of the excess anhydride is now removed by evaporation at 40°C/14 mms and the residual syrup is shaken up with water and diethyl ether. The diethyl ether is separated and the aqueous layer re-extracted with fresh diethyl ether, after which the combined diethyl ether layers are washed successively with 2-*N* acetic acid, aqueous sodium bicarbonate solution and water, dried over activated calcium sulphate and evaporated. The residue is now degassed by heating at 90°—100°C/0.1 mms for 20—30 minutes with occasional shaking. The product, 3-(2^1-formylamino-propyl)-indole (49.2 g $\equiv 0.243$ mols), is obtained in a 95.3% yield.

The last named compound is dissolved in dry tetrahydrofuran (300 mls) and added during 15 minutes to a stirred slurry of lithium aluminium hydride (18.5 $\equiv 2 \times 0.243$ mols) in dry tetrahydrofuran (100 mls). The mixture is cooled slightly during the addition and is protected by a nitrogen atmosphere. The reduction is completed by heating under reflux for 6 hours. The excess hydride is decomposed in the usual manner and the mixture is then filtered and the inorganic solids washed thoroughly with more solvent. The filtrate is evaporated and the residue dissolved in diethyl ether and extracted several times with 2-*N* acetic acid, the acid layer is washed once with fresh diethyl ether and is then made alkaline with 2-*N* sodium hydroxide solution. The resulting oily base is extracted with diethyl ether and the extract is washed with water, dried and evaporated to yield the crude product (*ca* 43 g). The latter can be crystallized from a mixture of equal parts of benzene and petroleum ether (b.r. = 60°—80°C) to yield 3-(2^1-methylamino-propyl)-indole as a white solid (25.2 g); m.p. = 90°—91°C. By evaporation of the mother-liquors, followed by distillation, a further quantity of the base may be obtained as a colourless syrup which boils at about 110°C/10^{-5} mms and which can be crystallized in the same way as the main yield.

EXAMPLE 2

3 - (2^1 - Amino - propyl) - indole (3.35 g $\equiv 0.0192$ mols) is added in portions to acetic anhydride (10 mls) and the resulting solution is heated on a steam-bath for 30—45 minutes. After removing excess acetic anhydride *in vacuo* the product is dissolved in ether and washed successively with dilute acid, sodium bicarbonate solution and water and then dried and evaporated. The residual 3-(2^1-acetylamino-propyl)-indole (2.85 g) is degassed as in the previous example.

The foregoing acetylated base is dissolved in dry diethyl ether (100 mls) and reduced with lithium aluminium hydride (1 g) in dry diethyl ether (100 mls) by heating under reflux for 5 hours. The product is worked up as described previously and, after distillation at 10^{-5} mms, is converted directly to 3-(2^1-ethylamino-propyl)-indole hydrochloride which crystallizes in white rosettes from ethanol/(ethyl acetate). It melts at 187°—189°C.

The manner in which the derivatives of the invention may be incorporated in pharmaceutical preparations is illustrated by the following.

The ingredients selected are: the product of example 1 (5 mg), lactose (110 mg), maize starch (55.2 mg), talcum (3.6 mg), magnesium stearate (1.2 mg) and distilled water (8.5 mg). The active material, namely the product of example 1, was sieved through a No. 60 sieve and the sieved material was mixed with the lactose and part of the starch. The remainder of the starch was formed into a paste with the distilled water and the paste was then mixed with the previously formed mixture containing the active material. The damp mass was then put through a Fitzmill machine and the resulting granules dried on trays in an oven at 40°C. The dried granules were then reduced by passage through a No. 16 sieve and mixed with talcum and magnesium stearate. The coated granules are then compressed on 8 mm punches into tablets having a double score (arranged so that each tablet can be broken into quarters).

WHAT WE CLAIM IS:—

1) 3 - (2^1 - Methylamino - propyl) - indole and pharmaceutically acceptable acid addition salts thereof.

2) 3 - (2^1 - Ethylamino - propyl) - indole and pharmaceutically acceptable acid addition salts thereof.

3) A process for the manufacture of the substances claimed in claim 1 and claim 2, which process comprises formylating or acetylating 3-(2^1-amino-propyl)-indole and reducing the carbonyl group of the resulting formyl or acetyl compound to the methylene group and, if desired, converting the resulting base into a pharmaceutically acceptable acid addition salt thereof.

4) A process in accordance with claim 3, wherein the indole starting material is treated with acetic acid anhydride or a mixture of acetic anhydride and formic acid and the

carbonyl group of the resulting acetyl or formyl compound reduced with lithium aluminium hydride.

5) A process for the manufacture of the substances claimed in claims 1 and 2, substantially as described with reference to the examples given.

W. D. WHITAKER,
Patent Agent,
for ROCHE PRODUCTS LIMITED.

PROVISIONAL SPECIFICATION

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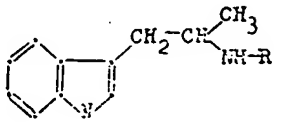

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